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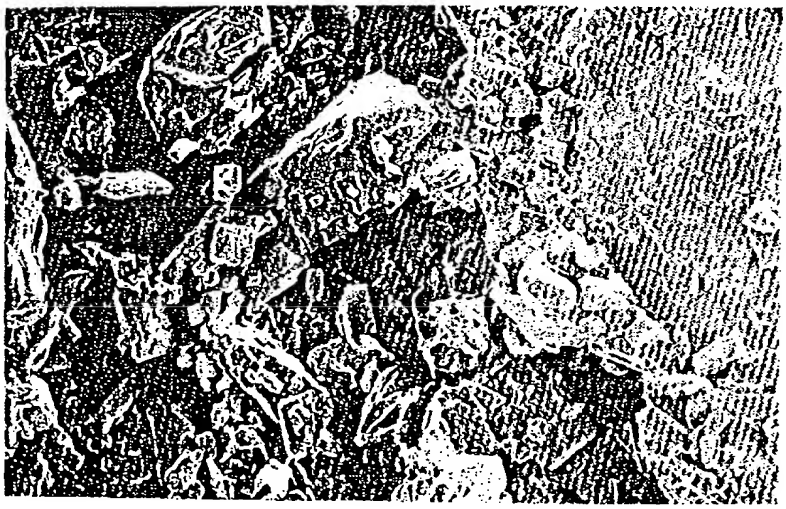

(57) Abstract

A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum-dried above the collapse temperature of the matrix. The matrix is preferably at least partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature instead of freeze drying it below its collapse temperature provides a process for producing tablets with commercially-acceptable structural strength and resistance to damage which rapidly disintegrates in normal amounts of saliva. The tablet preferably carries a drug, such as acetaminophen. The matrix network of the tablet preferably includes a gum, a carbohydrate and the drug. Especially preferred embodiments also include a flavoring, a sweetener and surfactant. The gum is preferably acacia, guar, xanthan, carrageenan or tragacanth gum. The carbohydrate is preferably mannitol, dextrose, sucrose, lactose, maltose, maltodextrin or corn syrup solids.

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IMPROVED RAPIDLY DISINTEGRATING TABLET

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention concerns pharmaceutical delivery forms, more particularly tablets for oral administration that disintegrate in an aqueous solution, such as saliva. The tablets disintegrate rapidly in the saliva of a subject's mouth, and can be swallowed easily without drinking water.

2. General Description of the Background

Lyophilization (which is also known as freeze-drying) is a technique for removing moisture from a wet material by freezing it and subsequently subliming moisture from it under reduced pressure. In this process, a suspension, solution or wet solid is frozen, and ice crystals in the frozen product are removed through a sublimation process at a reduced temperature and pressure that transforms ice directly into a vapor. The resulting freeze-dried product is a porous mass about the same size and shape as the original frozen mass. It has good stability, convenient reconstitutability when placed in solvent (usually water), and maintains flavor and texture similar to the original material.

Typical freeze-drying operations require three steps: freezing, removal of unbound liquid (primary drying) by sublimation from a solid directly into a vapor, and desorption of bound solvent (secondary drying) from a liquid into a vapor. Materials to be freeze-dried may be complex mixtures of solvent(s) and other substances that are cooled to form ice crystals. With further cooling, the mass becomes more rigid as the result of formation of eutectics. When the entire mass is solidified, all unbound solvent has been transformed into ice. Bound solvent, however, remains fixed as a liquid within the internal structure of the material and is not frozen.

During the sublimation phase of freeze-drying, the frozen material is exposed to a vacuum, and heat is applied to the ice crystals to sublime them. The temperature and pressure of the lyophilization process is carefully controlled such that the frozen mass is maintained below the eutectic temperature at which the mass begins to melt. Maintaining the temperature of the treated mass lower than its eutectic temperature is considered critical to providing a freeze-dried product. See, for example, U.S. Patent No. 4,616,047 and U.S. Patent No. 4,001,944, which stress that lyophilization occurs below the initial melting temperature of the mass. Removing unbound solvent during the primary drying step is therefore accomplished without exceeding the eutectic temperature of the composition. Direct sublimation from a solid to a vapor has been considered important to forming the microporous structure that gives freeze-dried products their porosity and reconstitutability.

Lyophilization processes have been used to prepare tablets that are described as rapidly dissolving in a subject's mouth. Such tablets are shown in U.S. Patent Nos. 4,371,516 and 4,946,684, as well as GB 2,111,423 and South African Patent Application No. 895546. These patents disclose pharmaceutical tablets having an open matrix network structure containing gelatin or a natural gum and a carbohydrate such as mannitol. U.S. Patent No. 4,946,684, for example, describes tablets containing mannitol and gum that are prepared by a lyophilization process in which the tablet is initially frozen. Moisture is then sublimed from the tablet below the initial melting temperature of the mixture. Direct sublimation of ice from the tablet has been found to produce a very porous open matrix network throughout the tablet into which saliva rapidly moves to disintegrate the lyophilized mass after it is placed in a subject's mouth.

Although the open matrix network of these lyophilized products produces a tablet that rapidly disintegrates in water or saliva, a serious drawback is that such tablets are very fragile, and their handling prior to placing in the mouth must be severely limited. This problem exists with respect to handling during manufacture, shipping the packaged product through normal distribution channels, and removal of the tablet from its packaging by the user. U.S. Patent No. 4,305,502 attempts to address this problem of the freeze-dried tablet's fragility by forming and lyophilizing the tablets in the depressions of a plastic blister package. The depressions are then covered by a peel-off sheet to seal the package and protect the tablets during storage. Even were this approach successful in reducing damage by the user, it does not address the issue of manufacturing tolerance and damage during shipping by vibration.

This fragile nature of freeze-dried products has largely rendered their widespread use impractical. Until now it has been thought that adequate tablet structural integrity was incompatible with obtaining a tablet that dissolves readily in the mouth.

Vacuum drying is an alternative method of removing liquid from a material by evaporating the liquid at a reduced pressure. Although vacuum drying is widely used in laboratory and industrial applications, it suffers from the drawback of producing explosive release of liquid from the material being dried. This explosive release disrupts the structure of the material, and has heretofore been considered unsuitable for commercial production of well formed or shaped products.

It is an object of the present invention to provide a process for producing improved rapidly disintegrating tablets that have enhanced structural integrity.

It is yet another object of the invention to provide an improved rapidly disintegrating tablet that does not survive the rigors of typical shipping conditions.

It is yet another object of the invention to provide such an improved tablet that rapidly disintegrates.

These and other objects of the invention will be understood more clearly by reference to the following detailed description and drawings.

SUMMARY OF THE INVENTION

The foregoing objects have been achieved in the present invention by disregarding prior tablet lyophilization processes in which solid unbound moisture is directly sublimed from a solid to a gas. The present inventors have instead prepared a rapidly disintegrating tablet by vacuum drying unbound liquid from a tablet matrix above the collapse temperature, where the collapse temperature is the initial melting point or eutectic temperature of the matrix. Vacuum drying above the collapse temperature during primary drying allows evaporation of free unbound solvent (such as water) to occur from a solid through the liquid phase to a gas under controlled conditions, instead of subliming from a solid directly to a gas as in lyophilization. When the matrix reaches its collapse point, the structure of the matrix partially collapses. The resulting vacuum dried tablet, as compared to a lyophilized tablet, has lower porosity, and is more resistant to damage by vibration or mechanical forces exerted on the tablet.

Vacuum drying preferably is performed throughout the primary drying stage at a temperature below the equilibrium freezing point of the composition, at which point the solvent (such as water) in the mixture changes phase. As the primary drying temperature reaches the equilibrium freezing point in a reduced pressure environment, local areas of structural disruption can occur due to eruption of liberated liquid from the

melting matrix. This problem is controlled by maintaining the temperature of the matrix during primary drying above the collapse temperature and below the equilibrium freezing point.

Vacuum drying uses subatmospheric pressure conditions to enhance removal of unbound solvent from the matrix during primary drying. Although any subatmospheric pressure will achieve this result, the present inventors have also found that it is preferable (although not required) to retard the phase change that occurs at the collapse point by selecting a suitable vacuum pressure, for example 0.5 to 10 torr. Such low pressures retard the rate of phase change occurring at the collapse temperature. Vacuum drying closer to atmospheric pressure (760 torr) results in a more rapid and complete phase change at the collapse temperature. The more controlled and slower phase change at low pressure is preferred because it produces a tablet having particularly good structural integrity. Hence, low pressures (e.g., 0.5-10 torr) are preferred in the vacuum drying chamber, particularly if the primary drying temperature is near the collapse temperature (e.g. 1-5°C above the collapse temperature). As the primary drying temperature approaches the equilibrium freezing point of the mass, local disruptions of the matrix may occur at higher pressures (for example higher than 10 torr) as local areas of solvent melt and the liquid is rapidly evolved from the tablet. Hence a lower pressure (for example 2.0 torr) is preferred as the temperature approaches the equilibrium freezing point (for example, from about 5°C below the equilibrium freezing point).

The tablet is a pharmaceutical dosage form suitable for oral administration as a solid that rapidly disintegrates in aqueous solution. The product has a partially collapsed matrix network containing a pharmacologically acceptable carrier material. The matrix has preferably been vacuum dried during primary

drying above the collapse temperature of the matrix. The matrix preferably includes a pharmaceutical compound which can be delivered and taste masked by the dissolving matrix. In preferred embodiments, the matrix contains a pharmaceutically effective amount of the active ingredient, 0.1-3.0% of a gum, and 10-60% of a carbohydrate base. All percentage weights throughout the specification and claims are dry weight when referring to a vacuum dried tablet (as here), and wet weight when referring to a formulation from which a tablet is made (as in Formulations 1-81). The gum is preferably selected from the group consisting of acacia, guar, xanthan, carrageenan, and tragacanth gum. The carbohydrate is preferably mannitol, dextrose, sucrose, lactose, maltose, maltodextrin, corn syrup solids, or mixtures thereof.

The active ingredient may be a particulate powder or crystalline material encapsulated as necessary, with a taste masking material such as partially hydrogenated cottonseed oil, corn oil, cellulose, flavored oil, zein, candied sugar, other encapsulating materials, or mixtures thereof. Many other pharmaceutical agents can be used in the tablet, including (without limitation) ibuprofen, caffeine, benzodiazepines, dextromethorphan cough suppressants, and veterinary medications. The tablet may also contain a flavor enhancer that further masks the taste of the drug, and a surfactant for enhancing dispersion of the ingredients and preventing adhesion of the tablet to the receptacle in which the tablet is formed.

In some preferred embodiments, the tablet comprises (by dry weight) an active ingredient in the amount of 1-60%, preferably 10-60% (without encapsulation), a carbohydrate base in an amount of 10-60%, a gum in an amount of 0.1-3.0%, 0.001-5.0% flavoring, less than 1% surfactant and less than about 1% sweetener. In particularly preferred embodiments, the tablet comprises 30-45% acetaminophen powder (not

including the weight of any encapsulation), 20-45% carbohydrate, and 0.1-0.5% (preferably 0.4%) gum. In other preferred embodiments, the tablet comprises 35% acetaminophen powder as the active ingredient, 40% mannitol, 0.4% xanthan gum, 0.3% mono-ammonium glycyrrihizinate sweetener, 0.15% aspartame, 1% wintergreen flavoring, and 0.01% nonionic surfactant. The tablets are preferably made from a formulation that is 25-35% w/w distilled water.

The present invention also includes a method of preparing a pharmaceutical tablet that can be orally administered and that disintegrates in an aqueous liquid solvent, such as saliva. The method includes the steps of preparing a mixture that includes sufficient amounts of water, gum and a carbohydrate to form a rapidly dissolving tablet. The mixture is formed into a desired tablet shape, frozen below its collapse point to form a solid matrix, and vacuum dried during primary drying above the collapse temperature, and preferably below the equilibrium freezing temperature of the mixture, to form the tablet. The tablet has a partially collapsed matrix that exhibits greater structural strength than its freeze dried counterpart, and reduced fragility. Thus, the tablets are produced with commercially-acceptable structural strength and resistance to damage. The shaped solid dosage form preferably contains a pharmaceutically active material that is distributed (preferably uniformly) throughout the dosage form.

The dosage form of the present invention preferably disintegrates in the mouth of a human or veterinary subject in twenty to sixty seconds.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a photomicrograph obtained with a scanning electron microscope (SEM) showing the partially collapsed matrix structure of a vacuum dried specimen of the tablet of the present invention at 500x magnification.

FIG. 2 is another SEM photomicrograph of the vacuum dried specimen (of Example V) at 500x magnification.

FIG. 3 is a photomicrograph obtained with a scanning electron microscope at 500x magnification showing the open matrix structure of a lyophilized tablet.

FIG. 4 is another SEM photomicrograph similar to FIG. 3 showing the matrix structure of the lyophilized specimen (of Example IV) at 500x magnification.

FIGS. 5-7 are differential scanning calorimetry (DSC) thermograms for four of the formulas of the present invention, showing how the collapse temperature of the mixture is determined.

FIG. 8 is a graph of sample temperature versus electrical resistivity showing changes in electrical resistance as the sample reaches its collapse temperature.

FIG. 9 is a graph showing shelf and tablet temperatures during vacuum drying of a matrix in accordance with the present invention.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

The pharmaceutical product of the present invention is a tablet that disintegrates rapidly in the mouth, provides adequate dosage levels of a drug, masks the taste of an active ingredient, and has sufficient structural integrity to withstand handling and vibration without substantial damage to the tablet. These advantages are achieved by forming a mixture (such as a slurry or paste) into a desired shape, freezing the mixture at a temperature that forms a solid matrix, then vacuum drying the matrix above its collapse temperature but below its equilibrium freezing temperature to form a partially collapsed matrix network. The mixture contains sufficient amounts of a gum, water and carbohydrate (as illustrated in the following examples) to form the solid frozen matrix that is then vacuum dried to form the tablet. The matrix network is

sufficiently porous to allow liquid (such as saliva in the oral cavity) to enter the pores of the tablet and cause rapid disintegration of the tablet.

Vacuum drying the matrix under the conditions described above results in the matrix being relatively or partially collapsed in comparison to the structure of the same matrix had it been lyophilized. Vacuum drying the mixture above its collapse temperature allows solvent in the mixture to evaporate from a solid through the liquid phase to a gas. This vacuum drying of moisture through a liquid phase, as opposed to sublimation of water by freeze drying from a solid phase, results in a partially collapsed matrix that has greater structural strength and is less fragile than freeze-dried tablets. The vacuum dried matrix has an increased mobility above the collapse temperature (as dissolved carbohydrate starts to fuse with other particles of carbohydrate and increasingly mobile solvent) to allow liquefaction to occur and permit evaporative primary drying of unbound water. The partially collapsed matrix of the present invention contrasts with the open matrix of lyophilized tablets in which direct sublimation of solvent leaves large pores. It is the open pore structure of the lyophilized matrix that makes such tablets more fragile, less dense and subject to damage than the partially collapsed matrix tablets of the present invention.

The tablets preferably contain an active ingredient, such as encapsulated acetaminophen, preferably (by dry weight) in a range of 1-60%, more preferably 10-60%. (These ranges do not include the weight of the encapsulating material). Although a lower percentage of acetaminophen ingredient can be used, a very low percentage may require an unacceptably large tablet to achieve a sufficiently therapeutic dosage of the drug. A percentage of drug higher than the preferred range can produce a product that is more difficult to pump as a liquid, and a tablet that has

unacceptably slow disintegration in aqueous solution. Very potent drugs can be present in small amounts, such as 10%, without making the tablet unacceptably large. When the active ingredient has a bitter taste, such as acetaminophen, that ingredient is preferably encapsulated with a material such as partially hydrogenated cottonseed oil, corn oil, flavored oil, zein (corn protein), cellulose and candied sugar. Encapsulation with one or more of these materials has been found to enhance the palatability of acetaminophen while the tablet is dissolving in the mouth.

The tablet also includes a carbohydrate base, such as mannitol, which provides structural integrity when the tablet is dry, and rapid disintegration in the presence of a liquid such as saliva. The carbohydrate base is preferably present in an amount of 10-60% dry weight. A lower percentage of carbohydrate base can reduce the structural integrity of the tablet and result in unsatisfactory organoleptic qualities. A percentage of carbohydrate above the preferred range produces a tablet that is large, denser, and dissolves more slowly. Some of the carbohydrates that have been found suitable for use in the present invention include dextrose, sucrose, lactose, maltose, maltodextrin, corn syrup solids, and combinations of sucrose/dextrose, corn syrup solids/mannitol, dextrose/mannitol, and maltodextrin/mannitol. However, the preferred carbohydrate is mannitol because it vacuum dries well, is not hygroscopic, and has a cool mouth feel due to its negative heat of solution.

A gum is used as a thickener in the mixture of the present invention. It serves to maintain the active ingredient in homogenous suspension and thereby achieve uniform distribution throughout the mixture. The gum also contributes to formation of the matrix, and provides a more palatable mouth feel of the tablet before and during disintegration. The gum is preferably present in the dry weight range of 0.1-3.0%. At least

0.1% of the preferred xanthan gum is preferred to keep the active ingredient in suspension. Xanthan and carrageenan gums have been found to be quite suitable for this purpose, although other gums that can be used include acacia, guar, and tragacanth gum. A maximum amount of 3.0% of gum is desirable to provide a tablet having a suitable mouth feel.

Especially preferred embodiments include a surfactant in the formulation to improve the flow qualities of the wet mixture and act as an emulsifier to prevent oil and water separation. A preferred surfactant has been found to be polysorbate 60, in an amount of 1.0% dry weight or less. Greater amounts of surfactant may produce an unpleasant taste. Successful embodiments of the present invention have been made without a surfactant.

Another optional ingredient of the present invention is a flavoring (for example, cherry or wintergreen). Flavorings may be used to provide an acceptable sensory appeal and mask bitterness. The flavorings are preferably used in an amount of .001-5.0% dry weight, but fruit powders, concentrates or purees can be used in higher amounts. In preferred embodiments, flavoring is any suitable natural, artificial or combined natural and artificial flavoring or flavor enhancer, such as maltol, ethyl maltol, citric acid, ascorbic acid or acetaldehyde.

Sweeteners are optionally used in the tablet to provide an acceptable sensory appeal and mask bitterness of an active ingredient. The range of amounts of sweeteners used varies substantially depending upon the identity of the sweetener. Artificial sweeteners are preferred because their potency allows a minimal amount of the sweetener to be present in the tablet. Some sweeteners that have been used in tablets of the present invention include acesulfame-K (SUNETTE), aspartame, sodium saccharin, calcium saccharin, and mono-ammonium glycyrrihizinate (MAGNASWEET or MAG). Mono-ammonium

glycyrrihizinate and aspartame are used as sweeteners in preferred embodiments of the invention described below. A desirable amount of the particular sweetener to be used can easily be determined. The tablet of the present invention may be made without a sweetener, because the sweetener is not important to formation of the drug carrying matrix. Unsweetened tablets are, however, less palatable.

The present invention will be better understood by reference to the following specific examples.

EXAMPLE I

A preferred embodiment of the rapidly disintegrating tablet of the present invention contains the following ingredients, designated formulation 1, with the respective amounts listed by wet weight.

Formulation 1

INGREDIENT	PERCENT
ENCAPSULATED ACETAMINOPHEN	35.00
MANNITOL	30.00
XANTHAN GUM	0.30
MONO-AMMONIUM GLYCYRRIHIZINATE	0.30
ASPARTAME	0.15
WINTERGREEN FLAVOR	1.00
POLYSORBATE 60	0.01
DISTILLED WATER	33.24

The encapsulated acetaminophen was Durkote APAP 145-75 obtained from Van Den Bergh Food Ingredients Group of Lisle, Illinois. The gum was Kelco Xanthan Gum K1B111. The flavoring was DM Wintergreen 1348.

The tablet formulation was made in a HOBART mixing bowl in which the required amount of water was placed at room temperature (24°C), and the mixer was turned on. The polysorbate was preheated to a flowable

liquid (30°C), and the required amount of liquid polysorbate was added to the water and mixed for 30-60 seconds. The Wintergreen flavor powder was then slowly added to the mixing solution until all lumps were dissolved. The aspartame and mono-ammonium glycyrrihizinate were next added to the mixing solution until all lumps were dissolved. Xanthan gum was then added and mixed in thoroughly, followed by mannitol, which was added to the solution and mixed until all lumps were dissolved. Finally, the encapsulated powdered acetaminophen was added to the mixing solution until all lumps were dissolved and a slurry mixture was formed. The mixer was then turned off, and the slurry from the mixing bowl was transferred into an intake tube. A 1.2 g amount of the mixture was deposited from the tube into one of the pre-formed indentations in a plastic blister pack to achieve a 325 mg acetaminophen dosage. The blister pack was obtained from Rexham Packaging of Orange, Connecticut, under product designation number 1025.

Vacuum drying was performed in an Edwards Lyoflex 1.8 vacuum dryer. The plastic blister pack was placed in a cold room at -40°C for 8 hours such that the mixture formed a frozen matrix in the indentation. The shelves of the vacuum dryer were then pre-chilled to -20°C, the blister pack containing the frozen tablets placed on the shelves, and the dryer door closed. A vacuum then was pulled to about 2.000 millibar (mbar), and maintained for 90 minutes to allow equilibration between the temperature of the frozen mixture and the dryer. Shelf temperature was then increased rapidly to +35°C. Shelf temperature and vacuum level was maintained at these levels for 4.0 hours to vacuum dry the product above the collapse temperature. The chamber was then purged with nitrogen gas to bring it to atmospheric pressure, and the blister pack removed from the dryer.

EXAMPLE II

The same formulation was used as in Example I, except the amount of mannitol was lowered to 23%. The tablets in the blister pack were frozen at -40°C for 8 hours to form a solid matrix, but the shelves of the vacuum dryer were pre-chilled to -47°C. The blister pack containing the frozen mixture was then placed on shelves, the dryer door was closed and the vacuum was pulled to less than 0.550 mbar, which was maintained for 90 minutes to allow equilibration between the temperature of the frozen mixture and the dryer. Shelf temperature was then increased rapidly to +35°C, and once the shelf temperature reached +35°C for 15 minutes, the vacuum was decreased to 2.000 mbar. Shelf temperature and vacuum level was maintained at these levels for 4.0 hours to vacuum dry the product at above the collapse temperature. The chamber was then purged with nitrogen as in Example I above.

EXAMPLE III

Electrothermal Analysis

The collapse temperature of the matrix can also be determined by electrothermal analysis in which the resistivity of the matrix is measured as a function of temperature. A graph of resistivity (in kilo-ohms) versus sample temperature for one of the tablets of the present invention is shown in FIG. 8. Resistivity for the tablet is shown as line 10, while resistivity of a reference ice sample is shown as line 11 for comparison. The slope of the resistivity plot changes markedly at about -25°C (illustrated by reference numeral 12 in the drawing), which is the collapse temperature at which the solid becomes more mobile and its resistivity drops. The resistivity of the tablet, which had been substantially the same as the resistivity of ice below -25°C, began to fall more rapidly than the resistivity of ice at temperatures above the collapse temperature. The point of divergence of lines 11 and 12 is at the collapse temperature.

The equilibrium freezing point (reference numeral 14) is also seen to occur at about -5°C. The free water (that is not chemically bound within the matrix) reaches its maximum mobility at this temperature due to its phase change, and resistivity of the matrix becomes substantially constant. Constant resistivity is indicated by line 10 flattening parallel to the temperature axis in FIG. 8. Some bound water remains within the matrix after primary drying, and will be removed during secondary drying above the equilibrium freezing point.

EXAMPLE IV

Lyophilized Reference Sample

This example provides information concerning a prior lyophilization process. The example is provided only for comparison purposes. Specifically, the formulation and protocol selected are as described by Blank (U.S. Patent No. 4,946,684), Example 1, for quick dissolving tablets.

In this example, the pharmaceutical substance is chlorpheniramine maleate and the natural gum component is a mixture of guar gum and acacia gum. The formulation for the dosage form is as follows:

INGREDIENT	QUANTITY % w/w
CHLORPHENIRAMINE MALEATE, USP	0.80
COLLOIDAL SILICON DIOXIDE, NF	0.40
MANNITOL, GRANULAR, USP	15.00
STARCH, PRE-GELATINIZED	1.00
GUAR GUM, MM	0.20
ACACIA GUM, NF	3.00
NUTRASWEET, NF	0.40
PROPYLPARABEN, NF	0.025
NAT. PEPPERMINT FLAVOR 410449	0.10
METHYLPARABEN, NF	0.075
DEIONIZED WATER, USP	79.0

The stepwise procedure for preparing a batch of suspension was as follows:

The deionized water was divided in a one-third portion, designated portion A, and a two-thirds portion, portion B. Portion A was heated to 75°C and the

methylparaben and propyl paraben were added slowly with stirring until dissolved. Separately the colloidal silicon dioxide was added to portion B and stirred until evenly dispersed. Portion A was then added to portion B. The temperature of the mixture rose to 30-40°C. Thereafter, the following ingredients were added sequentially, stirring each until dissolved: mannitol granules, the pregelatinized starch, Nutrasweet, chlorpheniramine maleate, acacia gum, and guar gum.

A 1.5 g amount of the mixture was deposited into each indentation of a pre-formed blister pack. The filled blister packs were placed in a cabinet freezer at -84°C. When the suspension was frozen, the samples were placed on the freeze dryer trays at a shelf temperature of -45°C. The condenser temperature was brought to between -55° and -65°C, and the vacuum was turned on to between 0.500 and 0.600 mbar. The heater was then turned on and the shelf temperature was adjusted to 50-55°C. The heat-dry cycle lasted for 4 hours. The vacuum, the condenser and the heater were turned off and the samples removed.

EXAMPLE V

Vacuum-Dried Reference Sample

In this example, the formulation and dosing of the suspension into the pre-formed blister pack are exactly as in Example IV, but the method of freezing and drying are that of the present invention.

Specifically, vacuum drying was performed in an Edwards Lyoflex 1.8 vacuum dryer. The plastic blister pack was placed in a cold room at -40°C for 8 hours such that the mixture formed a frozen matrix in the indentation. The shelves of the vacuum dryer were then prechilled to -20°C. The blister pack containing the frozen tablets was then placed on the shelves and the dryer door closed. A vacuum was then pulled to about 2.000 mbar and maintained for 90 minutes to allow equilibration between the temperature of the frozen mixture and the dryer. Shelf temperature was then

increased rapidly to +35°C. Shelf temperature and vacuum level were maintained at these levels for 4.0 hours to vacuum dry the product at above the collapse temperature. The chamber was then purged with nitrogen gas to bring it to atmospheric pressure, and the blister pack was removed from the dryer.

EXAMPLE VI

Determining Collapse Temperature With DSC

The collapse temperature of the frozen mixture was determined by differential scanning calorimetry (DSC). The thermograms were obtained with a DuPont 2000 DSC from E.I. DuPont de Nemours & Co. of Wilmington, Delaware. Deionized distilled water was used as a temperature calibration material. Temperature was calibrated so that the water peak was at 0°C. About 10 mg of sample material was sealed in an aluminum pan, and scanned from -60°C to +30°C at a rate of 3°C or 5°C/min. An empty pan was used as a reference, and three replicates were performed for each sample. All DSC thermograms were plotted on the same scale to compare the results for each sample with those of deionized distilled water.

Formulations 2, 3, 4 and 5 were prepared as in Example I using the following formulations listed by w/w:

FORMULATION	2	3	4	5
INGREDIENT (% w/w)	Flavor #1 Control %	Flavor #2 Control %	Flavor #3 Reduced %	Flavor #2 Reduced %
ENCAPSULATED ACETAMINOPHEN	35.00	35.00	42.00	42.00
MANNITOL	30.00	30.00	22.00	22.00
MALTRIN	--	--	2.00	2.00
XANTHAN GUM	0.30	0.30	0.30	0.30
MAG	0.30	0.30	0.30	0.30
ASPARTAME	0.15	0.15	0.15	0.15
FLAVOR #1	1.20	--	1.20	--
FLAVOR #2	--	1.20	--	1.20
POLYSORBATE 60	0.01	0.01	0.01	0.01
DISTILLED WATER	33.04	33.04	32.04	32.04
TOTAL	100.00	100.00	100.00	100.00
g wet mix/ 325 mg tablet	1.20	1.20	1.00	1.00

Formulation 6 is the formulation of Examples IV and V:

FORMULATION	6
INGREDIENT	QUANTITY % w/w
CHLORPHENIRAMINE MALEATE, USP	0.80
COLLOIDAL SILICON DIOXIDE, NF	0.40
MANNITOL, GRANULAR, USP	15.00
STARCH, PRE-GELATINIZED	1.00
GUAR GUM, MM	0.20
ACACIA GUM, NF	3.00
NUTRASWEET, NF	0.40
PROPYLPARABEN, NF	0.025
NAT. PEPPERMINT FLAVOR 410449	0.10
METHYLPARABEN, NF	0.075
DEIONIZED WATER, USP	79.0
TOTAL	100.00
g wet mix/tablet	1.50

The resulting thermogram for formulation 2 is shown in FIG. 5, while the thermogram for formulation 3 is shown in FIG. 6, and for formulation 4 in FIG. 7, and for formulation 6 in FIG. 8. A major endothermic peak

occurred in all formulation samples at about -0.5°C where solvent ice crystals changed phase from a solid to a liquid. This is the equilibrium freezing temperature, which is defined as the temperature at which the mobile solvent (in this case water) is in equilibrium with crystalline solvent. One exothermic peak occurred at about -15°C in formulations 4 and 5, but did not appear in formulations 2, 3 and 6. Another exothermic peak occurred at about -25°C in all formulations, which was believed to be due to dissolved mannitol changing from a solid to a dissolved solution of mannitol as mannitol particles started to fuse with each other and water molecules in local areas of increasingly mobile water. An exothermic peak is consistent with mannitol's negative heat of solution. Disturbance in the trace between -30 and -40°C in all formulations was probably due to a glass transition.

The collapse temperature of these formulations was concluded to be about -23°C for formulations 2-5, and -20°C for formulation 6, because that temperature coincided with the exothermic peak at the lowest temperature. The collapse temperature is the same as the eutectic temperature of a composition. The eutectic temperature is the lowest melting point of a composition, which in the above example is the temperature at which mannitol changes from a crystalline solid state to a liquid solution. The equilibrium freezing point of the composition corresponds to the temperature at which the crystals of the predominant solvent (in this case water) are in equilibrium with the liquid phase. Vacuum drying during the primary drying stage above the collapse temperature allows evaporation of unbound water to occur from a solid through a liquid phase to a gas under controlled conditions. As this phase change progresses, the matrix collapses as crystalline ice becomes more mobile. Maintaining the primary drying temperature below the equilibrium freezing point allows the tablet to be vacuum dried

without the explosive disruption that can occur in a vacuum dried product. Removal of moisture from the collapsed matrix leaves behind a dense microstructure that is described in Example VII.

EXAMPLE VII

Electron Photomicrographs

To evaluate the physical differences between lyophilized and vacuum dried rapid disintegrating tablets, scanning electron photomicrographs were obtained of both vacuum dried and lyophilized tablet specimens. Vacuum dried specimens are shown in the photomicrographs of FIGS. 1 and 2, while lyophilized specimens are shown in the photomicrographs of FIGS. 3 and 4. An examination of these structures shows that lyophilized specimens in FIGS. 3 and 4 have significantly larger pore diameters and less fused particles than the vacuum dried specimens of the present invention in FIGS. 1 and 2. The overall structure of the vacuum dried specimens of FIGS. 1 and 2 is much more uniform, with smaller pores and closed than in the lyophilized specimens of FIGS. 3 and 4. The photomicrographs of FIGS. 1 and 2 show a partially collapsed matrix network in the vacuum dried product, as opposed to the open matrix network in the lyophilized product of FIGS. 3 and 4.

The partially collapsed matrix network of the vacuum dried product of the present invention differs from a fully collapsed product, which would be a non-porous solid, such as dust or a solid tablet. Complete collapse of the matrix could be obtained by pressure crushing the tablet. Hence a partially collapsed matrix is at an intermediate point on a continuum from the open matrix lyophilized product to a crushed product having little or no matrix structure. Aside from the physical characteristics of a partially collapsed matrix that are described in this example and shown in FIGS. 1 and 2, a partially collapsed matrix is alternatively defined to be a matrix produced by vacuum drying the matrix at

least partially above the collapse temperature of the matrix, more preferably substantially completely above the collapse temperature, and most preferably completely above the collapse temperature. An example of drying at least partially above the collapse temperature of the matrix is removing about 50% of unbound moisture above the collapse temperature.

EXAMPLE VIII

Structural Strength

Resistance to Fracture

In this example, the products of Examples I (vacuum-dried), IV (lyophilized), and V (vacuum-dried) were subjected to a fracture test to measure their resistance to breaking in handling by the user. The fracture measurement was the pounds of force required to shear a tablet secured by a clamp. The instrument was a force gauge Model BG10 (Mark-10 Corp., Hicksville, NJ). Setting was Peak Tension with analog and digital filters disabled. Sample size was 30 for all samples. The mean results for each example are provided below.

Force required to fracture:

Sample	Mean	Std Dev
Example I (vacuum-dried)	0.162	0.030
Example IV (lyophilized)	0.105	0.026
Example V (vacuum-dried)	0.180	0.047

Probability matrix (statistical significance of results):

	Example I (vacuum-dried)	Example V (vacuum-dried)
Example IV (lyophilized):	100%	100%

These results demonstrate that the vacuum-dried tablets of the present invention are much more resistant to fracture than the lyophilized tablets of the prior art. These results are statistically significant at the 100% confidence level.

EXAMPLE IX

Structural Strength

Resistance to Vibration and Shock

In this example, the products of Examples I (vacuum-dried) and IV (lyophilized) were each cartoned and cased as for retail distribution. The packaged products then were subjected to an industry standard shipping test. Six cases of the product of Example I, and five cases of the product of Example IV were prepared. Eight (8) tablet blister packs were sealed with a peelable backing (26# CIS paper/PEL - 10.8#/R/48 ga PET/PEL 10.8#/R/100 ga Aluminum/3#/R Heat Seal Coating). The Sepha unit was then used to seal the blister packs, with a sealing temperature of 155°C, pressure of 6 bar, and a dwell time of 2.2 seconds. Two (2) blister packs were placed in each carton (2.53" X 0.69" X 4.44", James River 14 point SBS board), and 24 cartons were placed in each case (8 1/4" x 5 1/16" x 4 7/16", Weyerhaeuser 150 lb. board). The sample cases were subjected to ASTM Standard Test D4169-90, distribution cycle #3, at the laboratories of Weyerhaeuser Corporation in Tacoma, Washington, consisting of:

1) Standard climate conditions of 50% RH, 23 degrees C.
2) Manual handling - six point drop test on bottom, two bottom edges, two diagonal bottom corners, and top, all from 15 inches.
3) Loose-load vibration - shock simulation for a 40 minute dwell time:
   - Example I at a measured 13.7 frequency, 1.0 amplitude
   - Example IV at a measured 14.1 frequency, 1.0 amplitude
4) Vehicle vibration - shock simulation for a 10 minute dwell time:

- All cases at loose-load frequency and amplitude

5) Manual handling - six point drop test on bottom, two other bottom edges, two other diagonal bottom corners, and top - all from 15 inches.

After completion of distribution cycle #3, the tablets from each test group were visually inspected for damage.

Number of tablets damaged:

Sample	Tablets N	Damaged	Percent
Example I (vacuum-dried)	2304	1	0.04%
Example IV (lyophilized)	1920	15	0.78%

These results demonstrate that the vacuum-dried tablets of the present invention are much more resistant to shopping damage via vibration and shock than the lyophilized tablets made according to the teachings of the prior art. These results are statistically significant at the 100% confidence level.

EXAMPLE X

Porosity

In this example, the porosity of the products of Examples IV (lyophilized) and V (vacuum-dried) was measured. Scanning electron photomicrographs of sample tablets (cf: FIGS. 2 and 4) were digitized and analyzed for pore area as a percentage of total surface area on an image processing system (Krontron Model M14 SIMS-IPS) at the laboratories of the U.S. Bureau of Mines in Albany, Oregon.

The open matrix lyophilized product of Example IV had a porosity of 89% (i.e., 89% of the total surface area was pore openings). In contrast, the partially-collapsed matrix product of Example V had a porosity of 13% (i.e., 13% of the surface area was pore openings). These results illustrate the effects of vacuum drying

above the collapse temperature on the matrix structure of the tablet, where, under controlled conditions, the partially-collapsed matrix structure is formed characteristic of the present invention. This partially-collapsed structure, wherein the pores are partly closed, accounts for the structural strength and resistance to damage of the present invention.

EXAMPLE XI

Disintegration Time

In this example, the products of Examples IV (lyophilized) and V (vacuum-dried) were subjected to disintegration tests. Three testing methodologies were employed: unagitated disintegration time in warm water (the apparent method of U.S. 4,946,684), agitated disintegration time in warm water, and oral disintegration time in human subjects.

For the agitated method, a tablet is dropped into 40 ml of 37°C deionized water in a 250 ml Erlenmeyer flask being continuously agitated on an orbital shaker (Lab-Line Orbit) set at 200 rpm. End-point was defined to be complete disintegration of the tablet. Using this method, all products tested disintegrated rapidly, within 3 seconds.

For the unagitated method, a tablet is dropped into 50 ml of 37°C deionized water in a 100 ml beaker. End-point is complete disintegration of the tablet without manipulation. Disintegration times were likewise rapid with this method, all tablets again disintegrating completely within 3 seconds. These results are consistent with the findings of U.S. 4,946,684.

For oral disintegration measurement, each subject is given coded sample tablets and instructed to allow each tablet to disintegrate in the mouth without chewing or manipulation with the tongue. Subjects were asked to record the time in seconds required for the tablet to completely disintegrate. Using this method, the product of Example IV was found to disintegrate in

an average of 28 seconds, and the product of Example V in an average of 33 seconds. Although a difference in favor of the product of Example IV would be expected given its more open pore structure, the measured difference in the present example is not statistically significant. This suggests that surface pore area is not rate-limiting for the penetration of an aqueous solvent into these tablets within the range of surface porosities considered here.

Until now it has been though that adequate tablet structural integrity was incompatible with obtaining a tablet that disintegrates rapidly in the mouth. The foregoing results demonstrate that the vacuum-dried tablets of the present invention exhibit a desirable rapid rate of disintegration, comparable to lyophilized tablets, despite their structural strength and resistance to damage.

EXAMPLE XII

The tablet of the present invention can be formed by many different methods. The mixture can, for example, be placed in indentations on a freezing belt, drum or other device to form the tablet. Once the tablets are solidified, they may be removed and placed in bulk on a tray inside the vacuum dryer.

EXAMPLE XIII

Pharmaceutical and Chemical Ingredients

As used in this specification, a pharmaceutical dosage or delivery form is a tablet, suppository or other solid matrix intended for carrying a substance having therapeutic or diagnostic utility for living subjects, such as humans and animals. The pharmaceutical dosage form of the invention may be employed to administer a wide variety of pharmaceutical substances. Typical drugs that can be administered by means of this invention include, for example, anti-inflammatory agents, such as acetaminophen and ibuprofen; stimulants, such as caffeine; drugs for treating coronary disorders, such as digoxin; oral

vaccines; enzymes; peripheral vasodilators and anti-hypertensives, e.g. minoxidil; vasoconstrictors, e.g. ergotamine; analgesics; minor tranquilizers, e.g. lorazepam, oxazepam, diazepam; anti-depressants, e.g. desipramine; anti-convulsants, e.g. clonazepam; neuro-muscular drugs, e.g. pyridostigmine; hormones and oral contraceptives, e.g. ethynyl estradiol and norgestrel; corticosteroids, e.g. prednisolone; local anesthetics; spermicides, e.g. nonoxynol-9; anti-allergics, e.g. diphenhydramine and drugs relieving poisoning and metabolic dysfunction, e.g. methysergide.

The pharmaceutical dosage form is particularly useful for oral administration of drugs. It produces a convenient tablet that can be easily ingested without requiring drinking water. The tablet rapidly disintegrates in the oral cavity of humans and other mammals, making it ideal for administration to uncooperative subjects, such as geriatric, pediatric and veterinary patients. This form of administration can be used to administer drugs which are normally absorbed in the gastrointestinal tract, but is also useful for administration of substances (e.g. nitroglycerin) via the buccal or sublingual route because such drugs may be very rapidly absorbed by the use of the present invention.

In addition, the matrix of the present invention may be used to add a predetermined amount of chemical to an aqueous medium. For example, the chemical may be a diagnostic compound which is to be added to a biological sample, such as a sample of urine or blood, for determining the amount of a particular constituent present in the sample. Alternatively, it may be desired to add a predetermined amount of chemical reagent to a known amount of aqueous liquid to produce a standardized liquid which can be used, for example, in chemical analysis. The chemical may be a water-soluble or water-dispersible pharmaceutical which can be added to a known amount of aqueous medium to form a pharmaceutical

solution or dispersion which can be used for injection or inhalation. Certain chemicals are difficult or hazardous to handle in solution or suspension, and it may be desirable to convert them into a solid form which can be subsequently added to an aqueous medium to produce a solution or dispersion of the chemical. In all these instances, the matrix of the present invention disintegrates rapidly and disperses the chemical uniformly throughout the medium.

EXAMPLE XIV

Primary and Secondary Drying

The matrix of the present invention is dried during primary drying above the collapse temperature and preferably below the equilibrium freezing point of the matrix. Primary drying refers to the portion of the drying process during which substantially all crystalline unbound moisture is removed from the matrix. Primary drying can be distinguished from secondary drying by observing the temperature of the core of the matrix with a thermocouple. Primary drying ends and only secondary drying occurs when the core temperature of the tablet begins to rise rapidly, as evaporative cooling from primary drying is diminished. This relationship is illustrated in FIG. 9, which plots the progress of the drying process versus the temperature detected at the core of the tablet by a thermocouple.

A frozen tablet was placed in the vacuum dryer, and the shelf temperature increased to +35°C at the time indicated by reference numeral 16 in FIG. 9. The shelf temperature increased as shown by line 18, while the tablet temperature increased as shown by line 20. Both primary and secondary drying occurred simultaneously, as described below and shown in the legend on FIG. 9. During the primary drying stage, the temperature of the tablet increased from -25°C to about the -5°C equilibrium freezing temperature where removal of the mobilizing solvent occurred. After removal of the unbound water, primarily bound water remained for

removal. Bound water (which is always uncrystallized, even at temperatures that freeze the unbound water) is chemically bound within the matrix, for example, by hydrogen bonds. The temperature of the core of the product begins to rise rapidly after primary drying is completed.

As indicated by the legends in FIG. 9, both primary and secondary drying can occur simultaneously. Simultaneous primary and secondary drying occurs because, during the initial stage of vacuum drying, unbound water is removed from the outside of the tablet as a front of primary drying advances inwardly through the matrix. The temperature of the matrix behind the advancing front does not increase significantly because heat is used during primary drying to convert the ice crystals of unbound water from a solid through a liquid phase to a gas. The liquid is then evaporated under the reduced pressure conditions in the dryer. After the unbound water has been removed from behind the advancing front of primary drying, a front of secondary drying begins to advance through the tablet behind the first front. The temperature of the matrix begins to rise because the tablet is no longer cooled by the evaporation of unbound water in areas where secondary drying is now occurring. After the front of primary drying progresses completely inwardly through the core of the tablet, primary drying is complete. The temperature of the tablet rises rapidly as the vacuum drying process enters a stage in which only secondary drying occurs. The difference between primary and secondary drying is seen in FIG. 9 in which the core temperature of the tablet is substantially flat as primary drying occurs, but begins to curve upwardly when primary drying is complete.

As illustrated in the foregoing example and FIG. 9, primary drying is controlled to occur above the collapse temperature. All, substantially all, or at least a portion of primary drying may occur above the

collapse temperature. In especially preferred embodiments, primary drying is controlled to be completed by the time the tablet rises above the equilibrium freezing point of the matrix. It is not essential that all primary drying occur above the collapse temperature. Some sublimation drying may occur, for example, after a frozen tablet is placed in the vacuum dryer. Until the temperature of the tablet rises to the collapse temperature, some removal of bound moisture occurs by sublimation. Alternatively, primary drying may intentionally be performed partially below and partially above the collapse temperature. Such incidental or partial sublimation of unbound moisture is within the scope of this invention, as long as a sufficient amount of moisture is removed by vacuum drying above the collapse temperature to provide a partially collapsed matrix, preferably as shown in FIGS. 1 and 2.

Other examples of the tablet formulations are shown in the following Examples XV through XXVI.

EXAMPLE XV

Formulations 6-19

Ingredient (gm)	6	7	8	9	10	11	12	13	14	15	16	17	18	19
ACETAMINOPHEN	5.00	5.00	5.00	5.00	5.00	5	5	5	0.25	2.5	2.5	2.5	2.5	2.5
DEXTROSE	9.00	9.00	--	9.00	--	8	8	5.8	--	4.3	4.3	5	5	4.5
SUGAR	--	--	9.00	--	9.00	2	2	3	0.32	--	--	2	2	1.35
XANTHAN GUM	0.10	0.10	0.10	0.10	0.10	0.02	0.03	0.03	0.05	0.02	0.03	0.03	0.03	0.03
POLYSORBATE	0.02	0.02	0.02	--	--	--	0.02	0.05	0.05	0.02	0.02	0.02	--	0.02
MAG	0.10	0.10	0.10	--	.13(110)	0.1	--	0.1	0.03	0.09	0.1	0.1	0.15	0.1
ACESULFAME K	0.02	0.03	0.03	--	--	--	0.05	0.05	--	--	--	--	--	--
SACCHARIN	--	--	--	0.90	0.54	--	--	--	--	--	--	--	--	--
FLAVOR #1	--	--	--	0.30	--	0.4	0.7	0.5	0.1	0.1	--	0.12	--	--
FLAVOR #2	--	0.01	0.02	--	--	--	--	--	--	--	--	--	--	--
WATER	35.00	16.00	16.00	14.00	14	14	15.5	1.5	1.5	15	10	8.35	6.3	4.5
TOTAL	49.24	30.26	30.25	28.40	28.77	29.52	29.8	31		22.03	16.95	18.12	15.98	13
WET ING.	35.00	16.00	16.00	14.30	14.23	14.4	14.7	16		15.1	10	8.47	6.3	4.5
DRY ING.	14.24	14.26	14.25	14.10	14.54	15.12	15.1	14		6.93	6.95	9.65	9.68	8.5
# TABS	18	18	18	17	17	16	17	17		--				
WT./TAB	2.48	1.39	1.43	1.40	1.41	1.36	1.5	1.34		--		1.65	1.3	1.35
MG APAP	252	230	235	246	245	230	251	216		170		229	203	2.59

EXAMPLE XVI

Formulations 20-30

INGREDIENT (gm)	20	21	22	23	24	25	26	27	28	29	30
ACETAMINOPHEN	5.00	5	5	5	5	5	5	5	5	50	5
DEXTROSE	9.00	8.6	9	9	10	8	8	9	10	100	10
XANTHAN GUM	0.10	0.06	0.08	0.1	0.1	0.8	0.8	0.8	0.1	1	0.1
POLYSORBATE	0.02	0.04	0.02	0.02	0.02	0.02	0.02	0.02	0.04	0.4	0.02
MAG	0.10	0.2	0.15	0.15	0.15	0.2	0.2	0.3	0.5	5	0.2
ACESULFAME K	0.03	--	--	--	--	--	0.04	0.04	--		0.01
SACCHARIN	--	--	1.5	2.5	2	1	--	--	1	10	
FLAVOR #1	0.01	--	--	--	--	--	--	--			
FLAVOR #2	--	--	0.1	0.15	0.15	0.12	--	--	0.2	0.32	0.15
FLAVOR #3	--	--	--	--	--	--	0.3	0.35			
WATER	16.00	20	16.00	15.00	12	14	14	20	15	150	12
TOTAL	30.26	33.9	31.85	31.92	29.42	28.42	27.64	34.79	31.84	316.72	
WET ING.	16.00	20	17.50	17.50	14.00	15	14	20	16	160	
DRY ING.	14.26	13.9	14.35	14.42	15.42	13.42	13.64	14.79	15.84	156.72	
# TABS	18		18		16	16	13			30	
WT./TAB	1.39		1.42		1.39	1.47	1.66			1.95	
MG APAP	230		223		236	259	300			308	

The most preferred tablets obtained in Example XV were those prepared from formulations 6, 7 and 16. The tablets of formulations 18 and 19 were denser than desired. In Example XVI, the most preferred tablets were obtained from formulations 20-22, while formulation 24 produced a dense tablet. A high density tablet produces slower disintegration in the mouth.

The acetaminophen (APAP) in Examples XV and XVI was not encapsulated. In the following Example XVII, the acetaminophen was encapsulated. Amounts of gum, polysorbate and sweetener were also varied in this example, as indicated.

EXAMPLE XVII

Formulations 31-38

ENCAPSULATED ACETAMINOPHEN (75% APAP; 6.67 G = 5 G APAP AND 1.67 G COTTONSEED OIL)

INGREDIENT (gm)	31	32	33	34	35	36	37	38
ENCAPSULATED APAP	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67
DEXTROSE	9.00	8.6	9.00	9.00	9.00	8.6	8.6	8.6
XANTHAN GUM	0.10	0.06	0.10	0.10	0.10	0.06	0.06	0.06
POLYSORBATE	0.02	0.04	0.02	0.02	0.02	0.04	0.04	0.04
MAG	0.1	0.2	0.1	0.1	0.1	0.2	0.2	0.2
ACESULFAME K	0.05	--	0.03	0.03	0.03	--	--	--
FLAVOR #1	0.01	--	--	--	--	--	--	--
FLAVOR #2	--	--	0.15	0.15	0.15	0.15	0.15	0.15
WATER	16.00	20	18.00	20.00	22.00	19	18	17
TOTAL	30.26	35.57	34.07	36.07	38.07	34.72	33.72	32.72
WET ING.	16.00	20	18.00	20.00	22.00	19.00	18.00	18.00
DRY ING.	14.26	15.57	16.07	16.07	16.07	15.72	15.72	14.72
# TABS	18							
WT./TAB	1.39							
MG APAP	230							
RESULTS	BEST	BEST						

EXAMPLE XVIII

Formulations 39-48

Varying Carbohydrate, Flavoring and Sweeteners

INGREDIENT (gm)	39	40	41	42	43	44	45	46	47	48
REGULAR APAP OR	12.5	--	12.5	--						
ENCAPSULATED APAP	--	16.68	--	3.33	3.33	3.33	3.33	16.68	16.68	16.68
DEXTROSE	22.50	22.5	21.5				3.67		22.5	
LACTOSE				3.67						
M100						3.67		15		15
MALTOSE					3.67					
XANTHAN GUM	0.25	0.25	0.15	0.04	0.04	0.04	0.04	0.25	0.25	0.25
POLYSORBATE	0.05	0.05	0.1	0.01	0.01	0.01	0.01	0.05	0.05	0.05
MAG	0.25	0.25	0.5	0.05	0.05	0.05	0.05	0.25	0.25	0.25
SACCHARIN	2.5	2.5	--	0.5	0.5	0.5	0.5	2.5	2.5	2.5
FLAVOR	0.50	0.5	0.375	0.08	0.08	0.08	0.08		0.5	0.5
RASPBERRY PUREE								10		10
ACETALDEHYDE									0.08	0.08
WATER	40.00	40	50	9	9	9	9	35	40	35

The effect of different carbohydrate components was studied in this example. Lactose and maltose vacuum dried well, but had a less preferred mouth feel than dextrose. M100 is a maltodextrin that also dried well but produced a somewhat chalky mouth feel.

Raspberry puree and acetaldehyde were also used as flavoring agents in this example.

EXAMPLE XIX

Formulations 49-59

INGREDIENT	49	50	51	52	53	54	55	56	57	58	59
(ACTUAL APAP)	12.51	15.121%	12.51	19.230	22.5	26.25	15.15	30.00	29.05	29.996	22.500
ENCAPSULATED APAP	16.68	20.162%	16.68	25.642	30.000	35.00	20.20	--	35.00	36.140	30.000
DEXTROSE	22.50	27.197%	22.50	24.848	20.000	20.00	27.20	20.00	20.00	20.000	--
MANNITOL	--	--	--	--	--	--	--	--	--	--	20.000
XANTHAN GUM	0.25	0.302%	0.25	0.311	0.300	0.30	0.30	0.30	0.30	0.300	0.300
POLYSORBATE	0.05	0.060%	0.05	0.062	0.000		0.06	0.10	0.10	0.100	0.000
MAG	0.25	0.302%	0.25	0.311	0.300	0.30	0.30	0.30	0.30	0.500	0.300
SACCHARIN	2.5	3.022%	2.5								
ASPARTAME	--	--	--	0.124	0.15	0.15		0.15	0.15	0.200	0.150
MALTOL	--	--	--	--	--	--	0.25	1.00	0.50	0.200	--
FLAVOR #1	0.50	0.604%	--	0.621			0.60				
FLAVOR #2	--	--	0.025		0.03	0.03		0.05	0.05	0.060	0.030
WATER	40.00	48.350%	40.00	48.081	49.220	44.22	51.09	48.00	43.60	44.000	49.220
TOTAL	82.73	100.000%	82.255	100.00	100.00	100.00	100.00	99.90	100.00	101.50	100.00
WET ING.	42.50		42.50		49.22	44.22	51.09	48.00	43.60		
DRY ING.	40.23		39.755		50.78	55.78	48.91	51.90	56.40		
250 mg wet wt.	1.65		1.65	1.3	1.10	0.94	1.63	0.83	0.86	0.83	1.10
250 mg dry wt.	0.80		0.80								
500 mg wet wt.	3.30		3.30	2.6	2.2	1.88		1.66	1.72	1.66	2.20

APAP was encapsulated with cottonseed oil, except for formulation 10 in which APAP was encapsulated with corn oil. Taste masking with corn oil was not found to be as effective as taste masking with cottonseed oil.

Other tablet formations are shown in Examples XX and XXI.

EXAMPLE XX

Formulation 60

INGREDIENT	%	G/250 mg	G/325 mg	g/500mg
DEXTROSE	27.195%	0.449	0.584	0.897
ENCAPSULATED APAP	20.161%	0.333	0.433	0.665
FLAVOR #1	0.604%	0.101	0.013	0.020
XANTHAN GUM	0.302%	0.005	0.006	0.010
MAG	0.302%	0.005	0.006	0.010
CALCIUM SACCHARIN	0.066%	0.001	0.001	0.002
POLYSORBATE	0.060%	0.001	0.001	0.002
WATER	51.305%	0.847	1.102	1.693
TOTAL	100.000%	1.650	2.148	3.300

EXAMPLE XXI

Formulation 61

INGREDIENT	%	G/250mg	G/325mg	G/500mg
ENCAPSULATED APAP	35.000	0.333	0.434	0.665
STALEYDEX	20.000	0.190	0.248	0.380
XANTHAN	0.300	0.003	0.004	0.006
MAGNASWEET	0.300	0.003	0.004	0.006
ASPARTAME	0.150	0.001	0.002	0.003
FLAVOR	0.600	0.006	0.007	0.011
WATER	43.650	0.415	0.541	0.829
TOTAL	100.000	0.950	1.240	1.900

EXAMPLE XXII

In this example, APAP was encapsulated with varying amounts of zein (corn protein soluble in alcohol) as formulations 62-65.

Formulations 62-65

INGREDIENT (%)	X	.5 ZEIN 62	.7 ZEIN 63	1.0 ZEIN 64	1.0 ZEIN 65
ACTUAL APAP	26.25	26.25	26.25	26.25	26.25
ENCAPSULATED APAP	35.00	27.63	28.23	29.17	29.17
MANNITOL	20.00	20.00	20.00	20.00	25.00
XANTHAN GUM	0.30	0.30	0.30	0.30	0.30
CORN OIL	--	0.50	0.50	0.50	0.50
MAG	0.30	0.30	0.30	0.30	0.30
ASPARTAME	0.15	0.15	0.15	0.15	0.15
FLAVOR	0.60	0.60	0.60	0.60	0.60
WATER	43.65	50.52	49.92	48.98	43.98
TOTAL	100.00	100.00	100.00	100.00	100.00
g/ 250mg tablet		0.95	0.95		
g/ 325mg tablet		1.24	1.24		
g/ 500mg tablet		1.91	1.90		

EXAMPLE XXIII

Varying levels of mannitol were used in this example, as shown in formulations 66-69.

Formulations 66-69

INGREDIENT (%)	66	67	68	69
ACTUAL APAP	27.09	27.09	27.09	27.09
ENCAPSULATED APAP	35.00	35.00	35.00	35.00
DEXTROSE	20.00	--		
MANNITOL	--	20.00	25.00	25.00
XANTHAN GUM	0.30	0.30	0.30	0.30
MAG	0.30	0.30	0.30	0.30
ASPARTAME	0.15	0.15	0.20	0.15
FLAVOR	0.60	0.60	0.75	0.60
WATER	43.65	43.65	38.45	38.65
TOTAL	100.00	100.00	100.00	100.00
g/ 250mg tablet	0.92	0.92		
g/ 325mg tablet	1.20	1.20		
g/ 500mg tablet	1.85	1.85		

The most preferred tablet density in this example was obtained with formulation 68 at 25% mannitol.

EXAMPLE XXIV

Amounts of mannitol were varied in this example. Formulations 70-75

INGREDIENT (% w/w)	70	71	72	73	74	75
ACTUAL APAP	27.09	27.09	27.09	27.09	27.09	27.09
ENCAPSULATED APAP	35.00	35.00	35.00	35.00	35.00	35.00
MANNITOL	30.00	15.00	20.00	25.00	20.00	20.00
MALTRIN	--	15.00	10.00	10.00	5.00	--
XANTHAN GUM	0.30	0.30	0.30	0.30	0.30	0.30
MAG	0.30	0.30	0.30	0.30	0.30	0.30
ASPARTAME	0.15	0.15	0.15	0.15	0.15	0.15
FLAVOR	0.90	0.90	0.90	0.90	0.90	0.90
POLYSORBATE	0.01	0.01	0.01	0.01	0.01	0.01
WATER	33.34	33.34	33.34	33.34	33.34	33.34
TOTAL	100.00	100.00	100.00	100.00	100.00	100.00
g/ 250mg tablet	0.92	0.92	0.92	0.92	0.92	
g/ 325mg tablet	1.20	1.20	1.20	1.20	1.20	
g/ 500mg tablet	1.85	1.85	1.85	1.85	1.85	
approx dry wts						
g/ 325mg tablet	0.80	0.80	0.80	0.80	0.74	0.80
g/ 500mg tablet	1.23	1.23	1.23	1.23	1.23	

The most preferred tablet in this example was obtained with the control formulation 70 in which mannitol was present at 30%. This tablet had a good mouth feel, good density, effective taste masking, and good dissolution characteristics.

EXAMPLE XXV

Formulations 76-81

INGREDIENT (% w/w)	76	77	78	79	80	81
ACTUAL APAP	27.09		27.09	27.00	27.23	27.09
ENCAPSULATED APAP	35.00	70.00	35.00	--	25.50	35.00
MANNITOL	30.00	60.00	30.00	30.00	30.00	30.00
XANTHAN GUM	0.30	0.60	0.30	0.30	0.30	0.30
CARRAGEENAN						0.30
MAG	0.30	0.60	0.30	0.30	0.30	0.30
ASPARTAME	0.15	0.30	0.15	0.15	0.15	0.15
FLAVOR	1.00	2.00	0.90	0.90	0.90	0.90
ASCORBIC ACID	--		0.10	--	--	0.30
POLYSORBATE	0.01	0.02	0.01	0.01	0.01	0.01
WATER	33.24	66.48	33.24	41.34	40.84	33.04
TOTAL	100.00	200.00	100.00	100.00	100.00	100.00
g/ 325mg tablet	1.20		1.20	1.20	1.19	
g/ 500mg tablet	1.85		1.85	1.85	1.84	

Ascorbic acid was added as a flavor enhancer in formulations 78 and 81 of Example XXV. Carrageenan was substituted as a gum in formulation 81. Formulation 77 had no encapsulation for APAP, while formulations 78-81 used zein encapsulated APAP.

The foregoing examples illustrate a shaped solid dosage form, such as a tablet, having a partially

collapsed matrix containing therein a pharmaceutically active material that is distributed throughout the dosage form. A dosage form is a form (such as a tablet) for administering a dosage of a pharmaceutically active material. A pharmaceutically active material is a material that has a physiological or biological effect on an organism to which it is administered, and in particularly preferred embodiments is a therapeutic substance used to treat a pathological condition. The material is distributed throughout the dosage form or tablet as particles carried within the matrix. The material is preferably distributed substantially uniformly throughout the matrix, i.e. in substantially equal dosages per unit matrix. It is also possible to provide a concentrated dose in one region of the matrix.

Vacuum drying is preferably performed substantially completely below the equilibrium freezing point of the matrix, which means at least about 80% of the bound moisture, preferably 90%, most preferably about 100%, is removed from the matrix during primary drying below the equilibrium freezing point.

The present invention, in some very specific embodiments, also includes a method of dispensing tablets of the present invention from a blister pack by forcing them through a foil back on a blister pack. The invention also includes methods of administering the tablets to a subject (such as a human or animal) by placing the tablet in the oral cavity of the subject.

Having illustrated and described the principles of the invention in several embodiments, it should be apparent to those skilled in the art that the invention can be modified in arrangement and detail without departing from such principles. We claim all modifications coming within the spirit and scope of the following claims.

CLAIMS

1. A shaped solid dosage form having a partially collapsed matrix containing therein a pharmaceutically active material that is distributed throughout the dosage form.

2. The dosage form of claim 1 wherein the pharmaceutically active material is substantially uniformly distributed throughout the dosage form.

3. A shaped solid oral dosage form that rapidly disintegrates in aqueous solution, and which is an open matrix network carrying a pharmaceutically active material, wherein the matrix network has been vacuum dried to remove a matrix solvent at least partially above the collapse temperature of the matrix to form a partially collapsed matrix network and to enhance structural strength and resistance to damage.

4. The dosage form of claim 3 wherein the matrix network has been vacuum dried substantially completely above the collapse temperature of the matrix.

5. The dosage form of claim 4 wherein the matrix has been vacuum dried substantially completely below the equilibrium freezing point of the matrix.

6. The dosage form of claim 3 wherein the matrix comprises by dry weight 10-60% of a pharmaceutical compound, 0.1-3.0% of a gum, and 10-60% of a carbohydrate base.

7. The dosage form of claim 6 wherein the pharmaceutical compound is particulate acetaminophen.

8. The dosage form of claim 7 wherein the particles of acetaminophen are individually encapsulated with a taste masking material.

9. The dosage form of claim 6 further comprising a flavor enhancer and a surfactant.

10. The dosage form of claim 6 wherein the gum is selected from the group consisting of acacia, guar, xanthan, carrageenan, tragacanth gum and combinations thereof, and the carbohydrate is selected from the group consisting of mannitol, dextrose, sucrose, lactose,

maltose, maltodextrin, corn syrup solids, and combinations thereof.

11. The dosage form of claim 3 wherein the dosage form disintegrates in aqueous solution in ten seconds to one minute.

12. The dosage form of claim 3 further comprising a pharmaceutically active material distributed throughout the dosage form.

13. A vacuum dried pharmaceutical dosage form for oral administration as a shaped solid which comprises a matrix network that rapidly disintegrates in aqueous solution, wherein the dosage form comprises:

particles of a pharmaceutical compound individually encapsulated with a taste masking material;

a gum selected from the group consisting of acacia, guar, xanthan, carrageenan, tragacanth gum, and mixtures thereof; and

a carbohydrate selected from the group consisting of mannitol, dextrose, sucrose, lactose, maltose, maltodextrin, corn syrup solids, and mixtures thereof;

a solvent that is both bound and unbound in the matrix network;

wherein substantially all of the unbound solvent in the matrix has been vacuum dried during primary drying above a collapse temperature and below an equilibrium freezing point of the mixture to form a partially collapsed matrix network and to enhance structural strength and resistance to damage.

14. The dosage form of claim 13 having a matrix structure substantially as shown in the photomicrograph of FIG. 1.

15. A method of preparing a shaped pharmaceutical dosage form for oral administration as a solid that disintegrates in an aqueous solution, the method comprising the steps of:

preparing a mixture comprising a pharmaceutical carrier that forms a partially collapsed matrix network

when the mixture is vacuum dried above the collapse temperature of the matrix;

shaping the mixture into a desired pharmaceutical dosage form shape; and

vacuum drying the mixture above a collapse temperature of the mixture to form the partially collapsed matrix network.

16. The method of claim 15 wherein the mixture comprises a gum and a carbohydrate.

17. The method of claim 16 wherein the gum is selected from the group consisting of acacia, guar, xanthan, tragacanth gum, and mixtures thereof, and the carbohydrate is selected from the group consisting of mannitol, dextrose, sucrose, lactose, maltose, maltodextrin, corn syrup solids, and mixtures thereof.

18. The method of claim 15 wherein the vacuum drying step further comprises drying the mixture substantially completely below an equilibrium freezing point of the mixture.

19. The method of claim 15 wherein the mixture further comprises a pharmaceutically active compound.

20. The method of claim 15 wherein the preparing step comprises preparing a mixture comprising a pharmaceutically active material and a pharmaceutical carrier that forms a partially collapsed matrix network with the pharmaceutically active material distributed throughout the matrix after the mixture is vacuum dried above the collapse temperature of the matrix.

21. The method of claim 15 wherein the mixture has a collapse temperature of about -23°C.

22. The method of claim 17 wherein the mixture comprises (w/w) about 20-30% mannitol and .01-0.3% xanthan gum.

23. A method of preparing a shaped tablet for oral administration as a solid that rapidly disintegrates in an aqueous solution, the method comprising the steps of:

preparing a mixture comprising a pharmaceutically active material, and a pharmaceutical carrier containing a gum and a carbohydrate that forms a partially collapsed matrix network with the pharmaceutically active material distributed throughout the matrix when the mixture is vacuum dried above the collapse temperature of the matrix;

shaping the mixture into the form of a tablet; and

vacuum drying the mixture substantially completely above a collapse temperature of the mixture and substantially completely below an equilibrium freezing point of the mixture to form the matrix network.

24. A tablet comprising by dry weight:
an active ingredient in an amount of 10-60%;
a carbohydrate base in an amount of 10-60%; and
a gum in an amount of 0.1-3.0%;
wherein the active ingredient, carbohydrate base and gum have been blended together with a solvent to form a mixture that has been vacuum dried to remove unbound solvent above the collapse temperature of the mixture to produce a partially collapsed matrix network.

25. The tablet of claim 24 wherein the active ingredient is substantially uniformly distributed throughout the tablet.

26. The tablet of claim 24 further comprising a flavoring, sweetener and surfactant.

27. The tablet of claim 26 wherein the tablet comprises .001-5.0% flavoring, less than 1% sweetener and less than 1% surfactant.

28. The tablet of claim 24 wherein the active ingredient is powdered acetaminophen.

29. The tablet of claim 26 wherein the tablet comprises by dry weight 30-45% acetaminophen powder as the active ingredient, 30-45% mannitol, 0-3% maltodextrin, 0.4% xanthan gum, 0-1.0% sweetener, 0-2.0% flavoring, and 0.01% surfactant.

30. The tablet of claim 24 wherein the tablet has been vacuum dried at -20°C at 2.000 mbar for 15 minutes, and then at 35°C at 2.0 mbar for 4.0 hours.

31. A vacuum dried tablet having a partially collapsed matrix network structure substantially as shown in the photomicrograph of FIG. 1.

32. A product produced by the method of claim 15.

33. A method of orally administering a pharmaceutical material to a subject having an oral cavity, comprising the steps of:

preparing a mixture comprising a pharmaceutically active material and a pharmaceutical carrier that forms a partially collapsed matrix network with the pharmaceutically active material distributed throughout the matrix;

vacuum drying the mixture substantially completely above a collapse temperature of the mixture to form the partially collapsed matrix network; and

administering the dosage form to a subject by placing the dosage form in the oral cavity of the subject.

34. A method of administering a pharmaceutical material to a subject having an oral cavity, comprising the step of administering the dosage form of claim 15 to a subject by placing it in the oral cavity of the subject.

35. The method of claim 15 further comprising the step of retarding a phase change that occurs at a collapse point by vacuum drying below about 0.5 torr when a reaction temperature is within about 5°C above the collapse temperature of the matrix.

36. The method of claim 35 further comprising the step of vacuum drying above about 2.0 torr as the matrix temperature approaches the equilibrium freezing point.

37. The dosage form of claim 3 wherein the dosage form disintegrates in a mouth of a subject in twenty to sixty seconds.

38. The dosage form of claim 11 wherein the dosage form disintegrates in aqueous solution in one-half to one minute.

FIG. 1

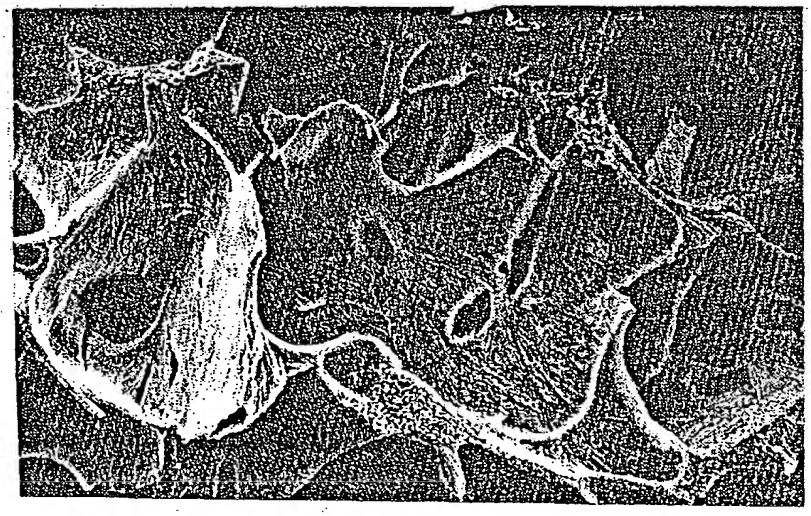

FIG. 2

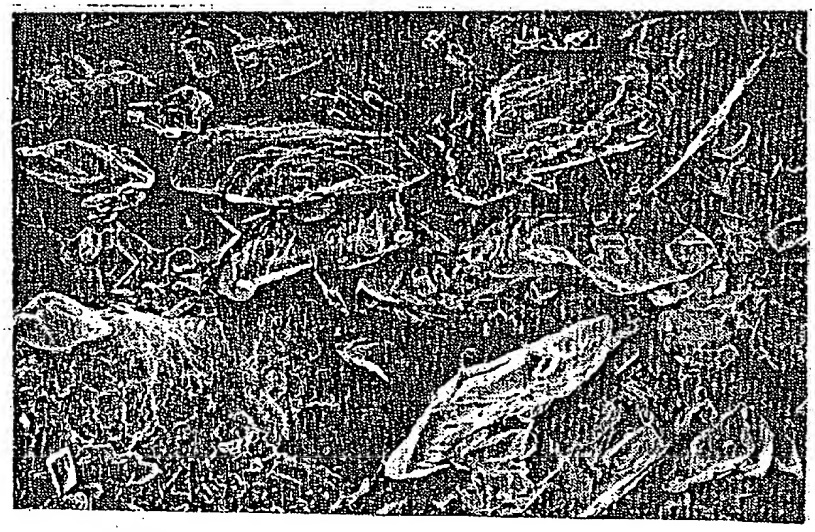

FIG. 3

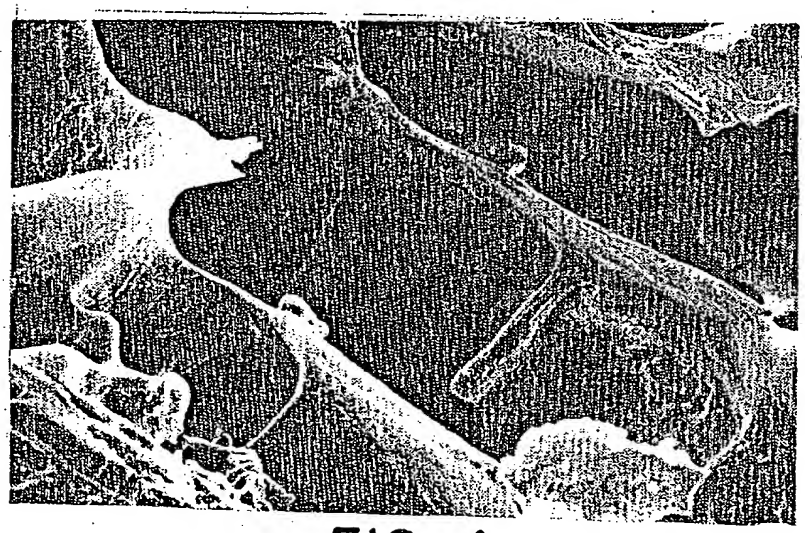

FIG. 4

FIG. 5

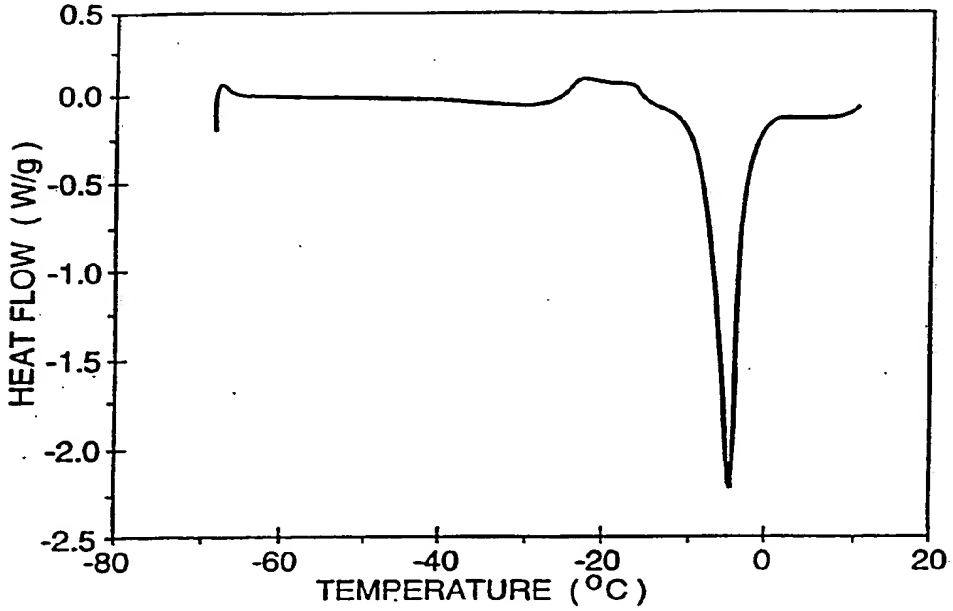
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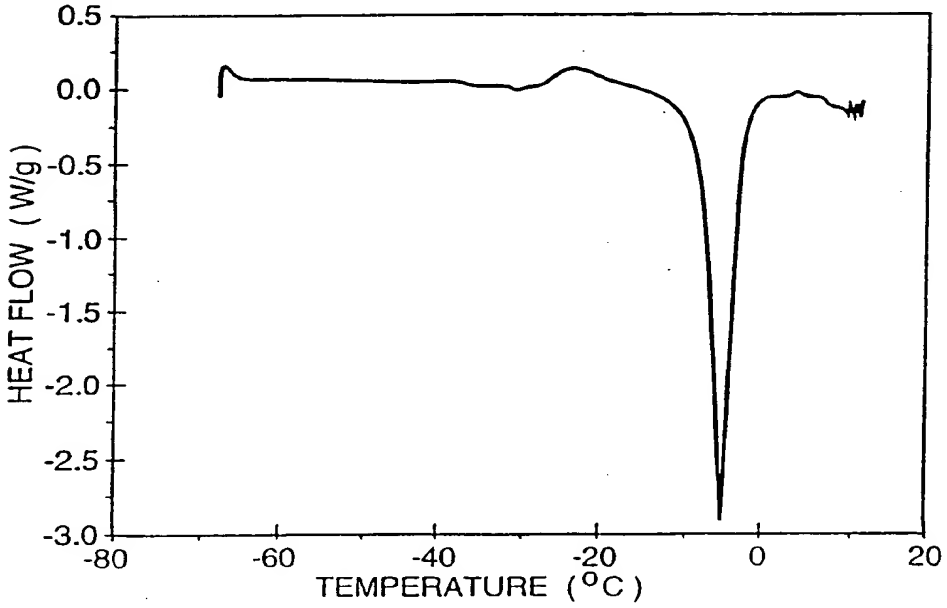
FIG. 6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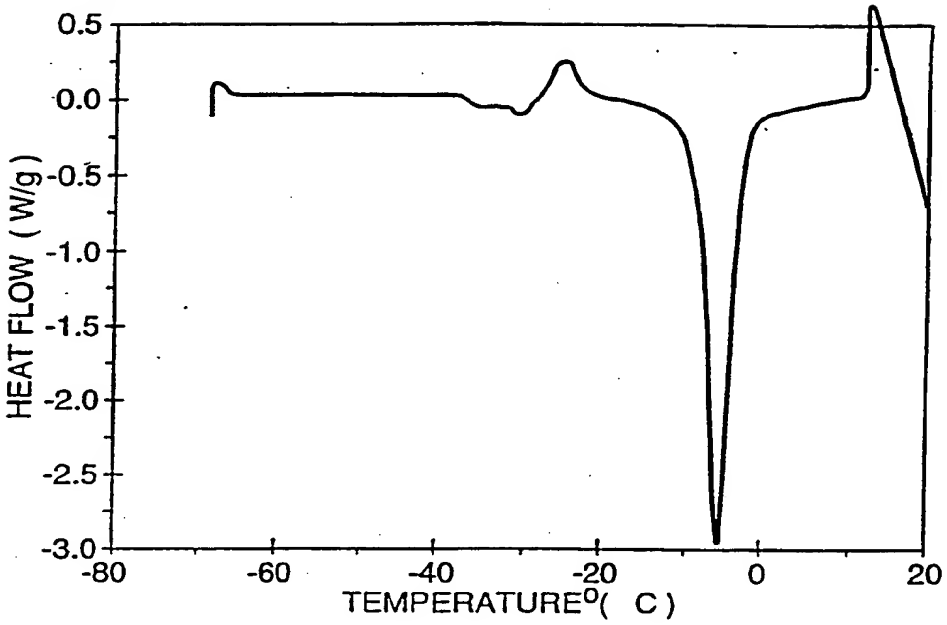
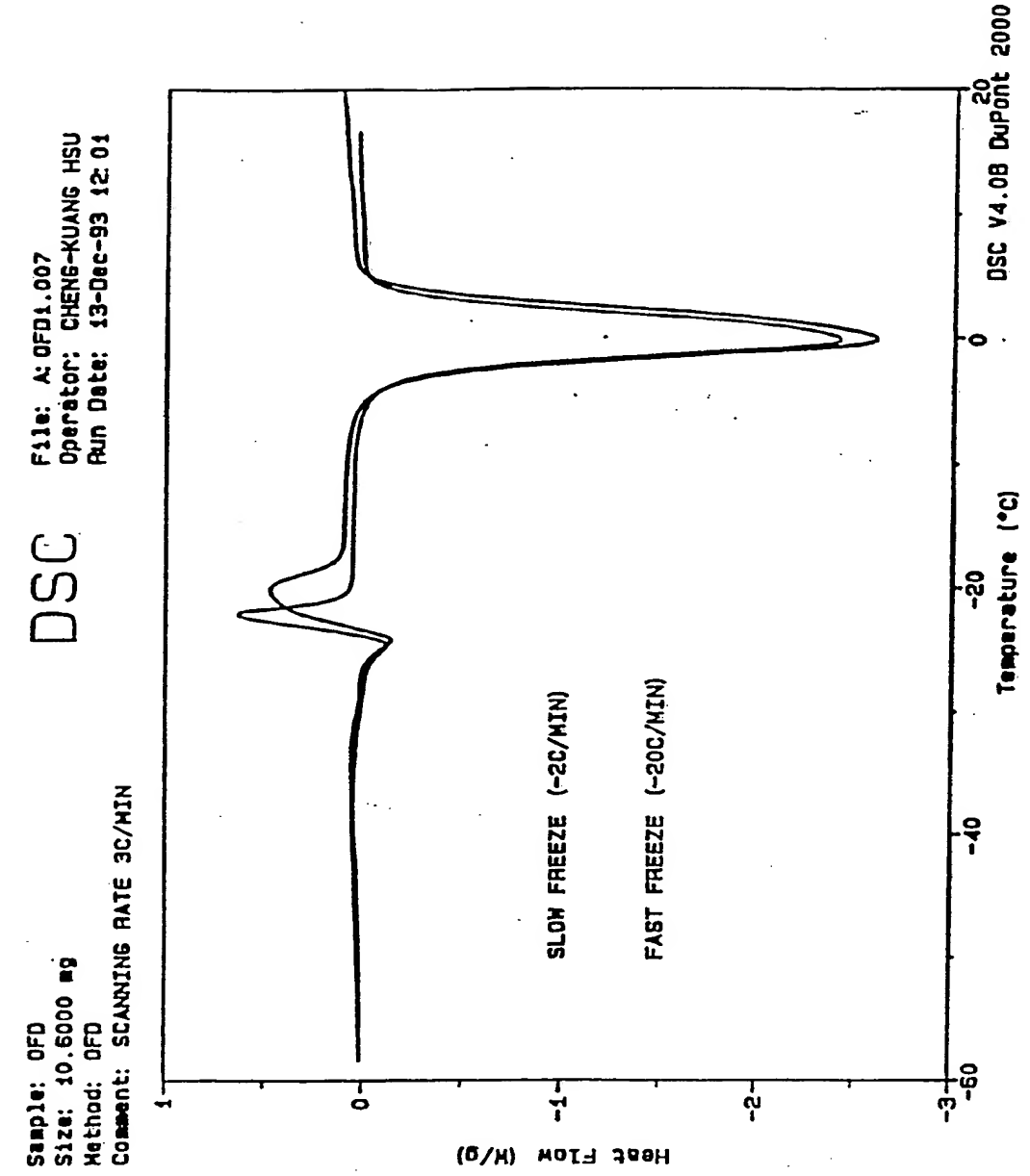
TEMPERATURE (°C)

FIG. 7

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FAST FREEZE (-20C/MIN)
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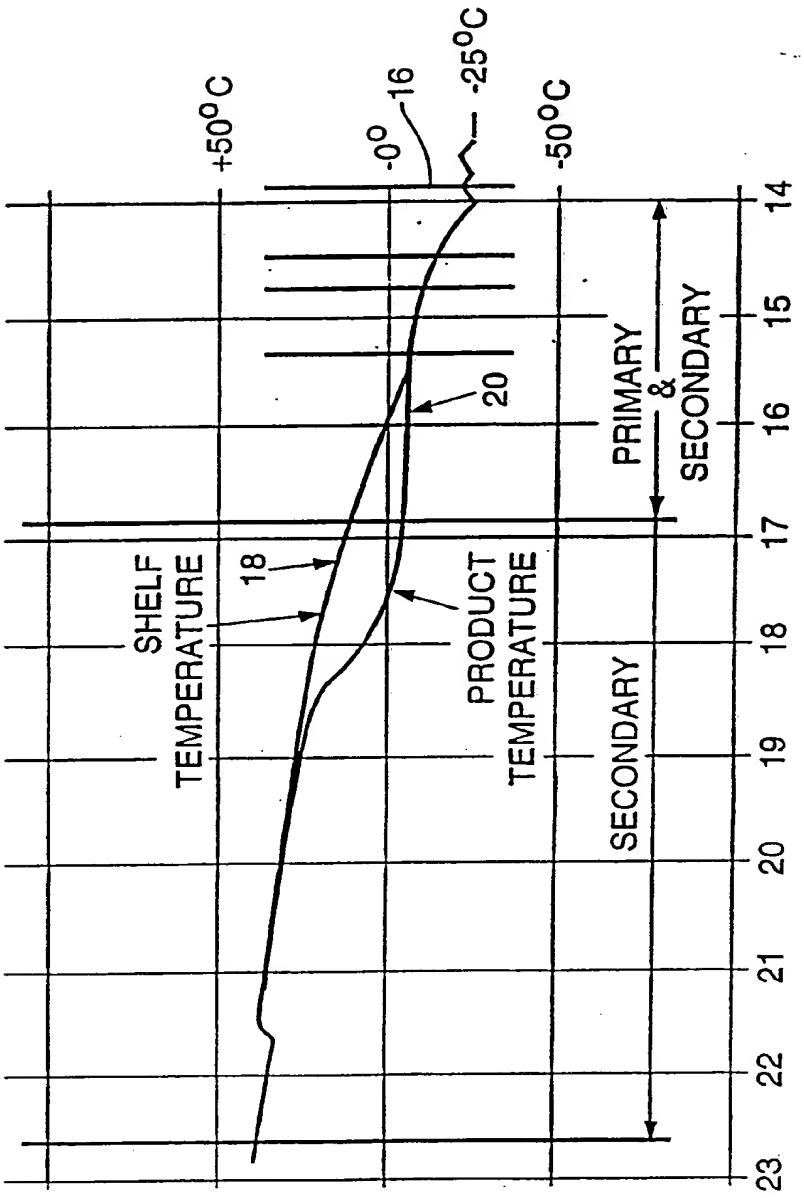
FIG. 8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SECONDARY
20
18
SHELF TEMPERATURE
PRODUCT TEMPERATURE

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12566

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 9/20
US CL :424/469, 484, 485, 488
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/469, 484, 485, 488

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,946,684 (BLANK ET AL) 07 AUGUST 1990. See particularly Example 1, col. 2 and col. 2,lines 15-50.	1-6, 10-12, 15-21, 23, 32-34 7-9, 13, 22, 24-29, 35-38
X, P Y, P	US, A, 5,215,756 (GOLE ET AL) 01 JUNE 1993. See particularly Examples 27 and 28 at col. 17, and col. 5, lines 19, 20, 25-27, 36, 37, 44-50.	1-5, 12, 15-21, 23-29, 32-34 6-11, 13, 22, 35-38
Y	US, A, 4,882,151 (YANG ET AL) 21 NOVEMBER 1989. See particularly col. 3, lines 22-36.	8, 13
A	US, A, 4,371,516 (GREGORY ET AL) 01 FEBRUARY 1983. See entire document.	1-38

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 02 MARCH 1994	Date of mailing of the international search report 11 APR 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer AMY HULINA Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*